

REMARKS

Claims have been cancelled and amended consistent with the election of claims and species required by the Office. With the amendments, claims 1, 2, 4-17 and 19-21 are pending. Applicants have amended the title of the invention as suggested by the Office, and herewith submit corrected formal drawings as required by the Office. All amendments are made without prejudice to refiling and do not constitute a narrowing of claim scope for purposes of patentability. No new matter has been added with these amendments.

As discussed below, the remaining claims are fully patentable. Applicants respectfully request prompt issuance of the pending claims.

I. 35 U.S.C. §112, First Paragraph Rejection

A. Claims 4-7 Are Enabled

Applicants request reconsideration of the rejection of claims 4-7 under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Office asserts that the instant application lacks any direction as to the practice of utilizing the G₁ beta strand of claim 4, since, it is urged, the G₁ beta strand is not defined in the disclosure. It is further stated that nowhere in the claims or the specification is there a clear explanation as to what exactly the G₁ beta strand is. (Paper No. 14, page 5).

Applicants traverse this ground for rejection. The invention, in fact, is straightforward and readily practiced by one skilled in the art, given the discoveries provided by applicants, without undue experimentation. As explained in the instant specification, it has been known that periplasmic chaperones, such as PapD, play an essential role in the building of pili, the hair-like adhesives important for bacterial attachment to host tissue. What was previously unknown was the precise three-dimensional structure and molecular interactions of a chaperone and a pilus submit co-complex. Applicants successfully crystalized the co-complex and provided an

altogether elegant elucidation of the molecular, three-dimensional interaction, especially the interaction of the G₁ beta strand binding with the cleft of the PapK. See Figures, particularly Fig. 2b. Armed with this new structural and molecular information, applicants have prepared molecular mimics, such as those of the G₁ beta strand which bind to PapK at the point of interaction and thereby inhibit pilus assembly, reducing (or eliminating) infection. Moreover, it is clear that multiple molecular mimics can be designed according to the guidelines provided by applicants, which mimics were not previously possible.

Accordingly, applicants respectfully submit that claims 4-7 are fully enabled when the specification, specific examples and the high level of knowledge in the art are considered. The specification describes both the content and the function of the G₁ beta strand of a chaperone and even provides examples of the G₁ beta strands of specific chaperones. The G₁ beta strand of chaperones is described generally as containing a conserved motif of solvent-exposed hydrophobic residues at positions 103, 105 and 107. The use of the G₁ beta strand containing these hydrophobic residues to complete the unfinished hydrophobic core of pilus subunits, such as FimH, is also described (page 28, lines 21-24).

Specific structural examples of G₁ beta strands are provided from the high resolution X-ray structures of the PapD/PapK and FimC/FimH co-complexes of the invention. The composition of the G₁ beta strand of a FimC chaperone is described on page 28, and the specific interaction between the G₁ beta strand of FimC and the strands of FimH, including the contacting of particular amino acid members of these strands is described on page 28-29 and illustrated in Figure 9A (page 28, line 27 - page 29, line 7). On page 46 of the application the content of the G₁ beta strand of a PapD chaperone is described on page 46. The amino acid sequence of a G₁ beta strand of a chaperone is described on page 46 as being in the N101 to L107 amino acid region, and the amino acid sequence of a G₁ beta strand of a PapD chaperone is described as being in the N101 to L107 amino acid region. A specific amino acid sequence for the amino acid sequence of a G₁ beta strand is even provided in SEQ ID NO: 1. The

function of a G₁ beta strand as the strand which is donated by the chaperone to complete the fold of the pilin domain is described on page 28 of the specification, a mechanism which is described as the donor strand complementation mechanism.

Specific working examples are supplied in the application that provide teaching and guidance with respect to the G₁ beta strand of chaperones. Example 1 is directed to the formation of crystals of the PapD-PapK Chaperone Subunit Co-Complex from which the specific information of the G₁ beta strand of the PapD chaperone is obtained. Similarly, example 4 is directed to the formation of crystals of the FimC-FimH Chaperone Subunit Co-Complex from which the specific information of the G₁ beta strand of the FimC chaperone is obtained. Example 6 is directed to a method of assessing the efficacy of mimics of the G₁ beta strand of chaperones; specifically, a method of determining the ability of FimH to bind to synthetic peptides corresponding to the G₁ beta strand of FimC C is described.

The Office admits that the Board in Ex parte Forman 230 USPQ 546 (BPA 1986) recognized that the level of skill in molecular biology is high. (Paper No. 4, page 5). Moreover, applicants have provided ample information in the specification in the form of description of G₁ beta strands, specific structural examples of G₁ beta strands, working examples directed to the identification of G₁ beta strands in co-crystal structures and methods to test the efficacy of mimics of G₁ beta strands.

Thus, applicants respectfully submit that the instant application provides ample direction as to the practice of utilizing mimics of the G₁ beta strand of claim 4 and claims 4-7 are fully enabled. Accordingly, applicants respectfully request the withdrawal of this rejection.

II. 35 U.S.C. §112, Second Paragraph Rejection

A. Claims 4-7, 12-15, 20 and 21 Properly Define The Invention

Reconsideration is requested of the rejection of claims 4-7, 12-15, 20 and 21 under 35 U.S.C. §112, second paragraph as being indefinite for assertedly failing to particularly and distinctly claim the subject matter which applicant regards as the

invention. The Office asserts that the metes and bounds of the (mimic) of the G₁ beta strand of claim 4 are not well defined within the instant claims. (Paper No. 14, page 5)

Applicants respectfully submit that the claims at issue are definite and do particularly and distinctly claim the subject matter which applicant regards as the invention. Claim 4 is directed to a compound which binds to a pilus subunit groove thereby inhibiting pilus assembly which further comprises a mimic of a chaperone G₁ beta strand having at least two alternating hydrophobic amino acid residues, the compound exhibiting activity against a Gram-negative bacterium.

Applicants respectfully submit that not only are the metes and bounds of the G₁ beta strand clear from the disclosure, the specification also teaches ways of determining still more information about numerous mimics of G₁ beta strands, including their interaction with pilin domains and effectiveness in preventing pilin assembly. A mimic of a chaperone G₁ beta strand is defined in the specification to be a substance that mimics or has the ability to bind to at least one pilus subunit in a manner which corresponds to the binding of a chaperone to a pilus subunit in the periplasmic space (page 21, lines 15-28). Various possibilities for the mimic are then described, including a modified or mutated form of the G₁ beta strand of the periplasmic chaperone at issue in the subject claims. As discussed above, both the structure and function of the G₁ beta strands are described at numerous places in the disclosure, and specific examples of the G₁ beta strands of certain chaperones are even supplied in the specification. Information has been provided with respect to the G₁ beta strand of specific periplasmic chaperones, such as FimC and PapD, on pages 28 and 46 of the specification. Furthermore, the examples of the application provide guidance as to the content of specific G₁ beta strands and their mode of interaction with other pilin domains (Example 5), and the methods in which it can be determined whether specific mimics thereof have the ability to exhibit antibacterial activity (Example 6). Since one skilled in the art could readily determine which compounds are included and excluded by the claims as worded, they appropriately define the invention, and this rejection should be withdrawn.

The definiteness provided by the specification with respect to the G₁ beta strand is also present with respect to the term "analog". The term "analog" is specifically defined on lines 1-14 of page 22 of the specification. Furthermore, the term "analog" is a well known term in the art and would be readily understood by anyone of ordinary skill in the subject art. A patent need not teach and preferably omits, what is well known in the art In re Buchner, 18 U.S.P.Q. 2d 1331, 1332 (Fed. Cir. 1991). Applicants submit that peptide analogs are commonly used by those of skill in the art and the use of the term "analog" in the application is defined in the specification, so that a skilled artisan would readily understand what is meant by an analog.

Accordingly, applicants submit that claims 4-7, 12-15, 20 and 21 are definite and do particularly and distinctly claim the subject matter which applicant regards as the invention and therefore request the withdrawal of this rejection.

III. **35 U.S.C. 102(b) Rejection**

A. *Marklund et al. Does Not Anticipate Claims 1, 2, 4-17 and 19-21*

Reconsideration is requested of the rejection of claims 1, 2, 4-17 and 19-21 under 35 U.S.C. 102(b) in view of Marklund et al. Marklund et al. discloses SEQ ID: NO 12 on page 2229, but only as a non-isolated portion of a long sequence of *E.coli* DNA. Moreover, this naturally-occurring sequence does not inhibit pilus assembly as required by claim 1, but rather it carries out pilus assembly. Claim 1 requires an isolated compound which inhibits pilus assembly, and is either a mimic of a G₁ beta strand or a mimic of an amino terminal motif of a pilus subunit, with at least two alternating hydrophobic amino acid residues or a 10 to 20 residue peptide or peptide analog of formula (I). Marklund et al. does not remotely anticipate or suggest this claimed invention.

A claim is anticipated only if each and every element as set forth in the claim is described in a single prior art reference. Verdegaal Bros. v. Union Oil Co. of Calif., 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987). See MPEP §2131. Therefore, since Marklund et al. does not disclose a mimic having the claimed features, Marklund et al. cannot

anticipate claim 1. Claims 2, 4-17, and 19 are also not anticipated by Marklund et al. because they incorporate the limitations of claim 1 by being dependent on claim 1 or dependent on a claim that is itself dependent on claim 1.

Claim 20 is directed to a mannose analog capable of competitively binding the amino terminal mannose-binding domain of a Gram-negative bacterial adhesin. SEQ ID: NO 12 consists of 10 amino acid residues; it is a peptide, not a carbohydrate analog. Consequently, Marklund et al. does not remotely anticipate claim 20 or claim 21, which is dependent from claim 20.

B. Kuehn et al. Does Not Anticipate Claims 1, 2, 4-7

Reconsideration is requested of the rejection of claims 1, 2, 4-17 and 19-21 under 35 U.S.C. 102(b) in view of Kuehn et al. The Office asserts that any of the peptides disclosed in Kuehn et al. would anticipate claims 1, 2 and 4-7 because the definition of analogue is ambiguous (Paper No. 4, page 7).

The term analog is defined on lines 1-14 of page 22 of the specification and is a well known term in the art that would be readily understood by anyone of ordinary skill. A patent need not teach and preferably omits, what is well known in the art. In re Buchner, 18 U.S.P.Q. 2d 1331, 1332 (Fed. Cir. 1991). A claim is anticipated only if each and every element as set forth in the claim is described in a single prior art reference. Verdegaal Bros. v. Union Oil Co. of Calif., 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987). See MPEP §2131. Kuehn et al. is directed to an investigation of the structural basis for PapD's interaction with pilus subunits and various peptides used in this investigation are disclosed. However, nowhere in Kuehn et al. are disclosed particular compounds which bind to a pilus subunit groove and thereby inhibit pilus assembly. The Office's objection to the term analog, a term readily understood by those of skill in the art, simply cannot provide this absent disclosure.

IV. 35 U.S.C. 103(a) Rejection

Reconsideration is requested of the rejection of claims 1, 2, 4-17, and 19-21 under 35 U.S.C. 103(a) in view of Kuehn et al. For the reasons detailed below, this rejection is not supported by the cited art.

To properly support a determination of obviousness, the rejection must be based upon what the prior art would have led one skilled in the art to do. The courts have consistently held that the test for a prima facie case of obviousness is not whether an invention is obvious to try. In re O'Farrell, 7 U.S.P.Q.2d 1673, 1680-1681 (Fed. Cir. 1988). The prior art must suggest the modification and provide a reasonable expectation of success if the modification is made. Id.; In re Dow Chem., 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988); MPEP §2142 (p.2100-89) and §2143.02 (p. 2100-92). Furthermore, the prior art reference must teach or suggest all the claim limitations.

Kuehn et al. is directed to an investigation of the basis for PapD's interaction with pilus subunits. The Office points to the discussion of the binding of the PapD chaperone to the COOH-terminal peptides from pilus subunits on pages 1235-1236 as providing motivation to make the modifications as stated in claim 6 and 9 (Paper No. 4, page 8). The discussion on pages 1235-1236, however, is directed to investigations of the role of the conserved COOH-termini of the pilus subunits in chaperone binding. The peptides that were synthesized corresponded to the 19 residues at the COOH-terminus of the P pilus subunit of various proteins, PapG, PapE, PapF, PapK and PapH. PapD was used to determine how well PapD as a chaperone could bind these synthetic peptides. The Office also points to the final paragraph of page 1240 as "motivating the instant invention *in the context* of chaperones" (emphasis added) Id. This paragraph, however, properly identifies the focus of the article as being an investigation of the mode of chaperone binding and the structural basis therefore, "... the mode of chaperone binding described in this article actually presents a "snapshot" of a process fundamental to Gram-negative pathogens." The reference to the details of the chaperone-adhesion interaction "*may lead to the design of high affinity synthetic inhibitors which would prevent pilus assembly*" (emphasis added) is merely speculative. The statement is also extremely vague; no guidance, teaching or direction is provided

by the Kuehn et al. article beyond this speculation. The discussion on pages 1235-1236 certainly provides no guidance as it is directed to an investigation of the role the COOH-termini of the pilus subunits plays in chaperone binding. No suggestion is made in conjunction with this discussion of the COOH-termini of the pilus subunits that compounds - much less, which compounds, can be made which will actually inhibit pilus assembly.

Even assuming, arguendo, that the vague and speculative statement in the final paragraph of page 1240 of Kuehn et al. would have motivated a skilled artisan to "try" to make the specific compounds of the invention, Kuehn et al. do not provide a reasonable expectation that any such compounds would have the claimed ability to inhibit pilus assembly. The reference simply would not have allowed one skilled in the art to anticipate with any degree of certainty the now-demonstrated utility of the compounds of claims 1, 2, 4-17, and 19-21.

Because the only references relied upon by the Office do not teach or suggest the claimed compounds, the Office appears to be applying "hindsight reconstruction" by using the teaching of the Applicants' patent application as a guide for searching, and analyzing the references in the right way to arrive at the claims at issue. Such hindsight reconstruction is clearly contrary to the law. The prima facie burden of establishing that the claims would have been obvious to a skilled artisan has not been met. Accordingly, Applicants respectfully traverse this basis for rejection of claims 1,2, 4-17, and 19-21 and request its reconsideration and withdrawal.

VERSION WITH MARKINGS SHOWING CHANGES MADE

IN THE TITLE

ANTIBACTERIAL COMPOUNDS DIRECTED AGAINST PILUS BIOGENESIS,
ADHESION AND ACTIVITY[; CO-CRYSTALS OF PILUS SUBUNITS AND METHODS
OF USE THEREOF]

IN THE CLAIMS:

1. (once amended) An isolated compound which [binds to a pilus subunit groove thereby inhibiting] inhibits pilus assembly, said compound comprising a mimic of a chaperone G, beta-strand with at least two alternating hydrophobic amino acid residues or a 10 to 20 residue peptide analog according to formula (I):

5 (I) $Z_1 \sim Z_2 - X_1 - X_2 - X_3 - X_4 - X_5 - X_6 - X_7 - X_8 - X_9 - X_{10} - Z_3 \sim Z_4$
or a pharmaceutically-acceptable salt thereof, wherein:

Z_1 is R-C(O)-NR- or RRN-;

Z_2 is an optional 1 to 5 residue peptide or peptide analog;

X_1 is any amino acid residue;

10 X_2 is any amino acid residue;

X_3 is a hydrophobic residue or a hydroxyl-substituted aliphatic residue;

X_4 is any amino acid residue;

X_5 is a hydrophobic residue or Gly;

X_6 is a hydrophobic or a hydrophilic residue;

15 X_7 is Gly, an amide-substituted polar residue or a hydrophobic residue;

X_8 is any amino acid residue;

X_9 is an aliphatic residue;

X_{10} is any amino acid residue;

Z_3 is an optional 1 to 5 residue peptide or peptide analog;

20 Z_4 is -C(O)OR or -C(O)NRR;

each R is independently hydrogen, C₁-C₆) alkyl, C₂-C₆) alkenyl, C₂-C₆) alkynyl or C₆-C₁₄) aryl;

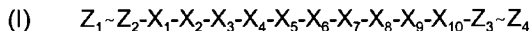
each "-" between residues X₁ through X₁₀, Z₂ and X₁ and X₁₀ and Z₃
independently represents an amide linkage, a substituted amide linkage or an isostere
25 of an amide linkage; and

each "~" represents a bond.

4. (once amended) The compound of claim 1 [further comprising] wherein the mimic comprises a mimic of a chaperone G₁ beta-strand with at least two alternating hydrophobic amino acid residues which exhibits antibacterial activity against a Gram-negative bacterium.

8. (once amended) The compound of claim 1 [further comprising] wherein the mimic comprises a mimic of an amino-terminal motif of a pilus subunit [with at least two alternating hydrophobic amino acid residues which mimic exhibits antibacterial activity against a Gram-negative bacterium] selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28 and SEQ ID NO: 29.

12. (once amended) The compound of claim 1 which is a 10-20 residue peptide or peptide analog according to formula (I):



or a pharmaceutically-acceptable salt thereof, wherein:

5 Z₁ is R-C(O)-NR- or RRN-;

Z₂ is an optional 1 to 5 residue peptide or peptide analog;

X₁ is any amino acid residue;

X₂ is any amino acid residue;

X₃ is a hydrophobic residue or a hydroxyl-substituted aliphatic residue;

10 X₄ is any amino acid residue;

X₅ is a hydrophobic residue or Gly;

X₆ is a hydrophobic or a hydrophilic residue;

X₇ is Gly, an amide-substituted polar residue or a hydrophobic residue;

X₈ is any amino acid residue;

15 X₉ is an aliphatic residue;

X₁₀ is any amino acid residue;

Z₃ is an optional 1 to 5 residue peptide or peptide analog;

Z₄ is -C(O)OR or -C(O)NRR;

20 each R is independently hydrogen, (C₁-C₆) alkyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl
or (C₆-C₁₄) aryl;

each "-" between residues X₁ through X₁₀, Z₂ and X₁ and X₁₀ and Z₃
independently represents an amide linkage, a substituted amide linkage or an isostere
of an amide [likage] linkage; and

each "~" represents a bond.

14. (once amended) The compound of claim 13 which is selected from the
group consisting of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ
ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO:
11, [SEQ ID NO: 12,] SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO:
5 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21,
SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26,
SEQ ID NO: 27, SEQ ID NO: 28 and SEQ ID NO: 29.

Claims 3, 18 and 22-135 are cancelled.

CONCLUSION

Favorable consideration and early allowance of all pending claims is requested.
Please contact the undersigned with any questions.

The Commissioner is hereby authorized to charge Account No. 19-1345 any fees under 37 CFR 1.16 and 1.17 which may be required during the entire pendency of this application.

Respectfully submitted,



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